

## New insights into DMD using mouse and canine models

Two research articles published in the current issue progress our understanding of Duchenne muscular dystrophy (DMD), a debilitating X-linked disorder characterised by progressive muscular weakness and degeneration. The disorder is caused by mutations in the gene encoding dystrophin, an important component of the dystrophin-glycoprotein complex (DGC) that connects intracellular proteins with the extracellular matrix and promotes muscle fibre integrity. In the first of the two studies, Mariz Vainzof and colleagues report a new mouse model for the disease in the form of a *Dmd*<sup>mdx</sup>/*Large*<sup>myd</sup> double mutant (page 1167). In addition to lacking dystrophin, this mouse also expresses a mutated version of the gene encoding LARGE, another important component of the DGC. The combination of these two mutations provides a model that demonstrates a



Dean Burkin's group thank Scott Barnett, Department of Pharmacology, University of Nevada, Reno, NV, for his assistance in producing the image.

severe neuromuscular phenotype and accurately mimics the symptoms of human muscular dystrophies. The authors also demonstrate that the model could be used to test the benefit of stem cell therapy to treat DMD and associated disorders. In a second study, Dean Burkin's group provides insight into the mechanism underlying the beneficial effects of corticosteroid therapy in DMD and reveal potential candidates to target in future therapeutic approaches that might overcome the negative side effects associated with steroid use (page 1175). In their work, they utilise *in vitro* cultured myogenic cells and also a canine model of DMD that shows strong phenotypic similarities to human DMD patients, demonstrating that the use of multiple complementary approaches and model systems can allow complex disease mechanisms to be elucidated.

## Reproducing the physiological environment of HIV infection



Acquired immunodeficiency syndrome (AIDS), caused by human immunodeficiency virus (HIV) infection, is characterised by increased vulnerability to potentially life-threatening infections. Although there are treatments that can impede progress of the disease, there are no cures or vaccines. The most common route for transmission of the virus is via heterosexual intercourse. The animal models that are currently available do not accurately replicate the physiological environment of vaginal intercourse, so the effects of factors such as seminal fluid composition on HIV infectivity have not been thoroughly examined. Here, Mary Jane Potash and colleagues describe a system for reproducible and efficient sexual transmission of HIV in mice. Using this model, the group show that the rate of viral transmission dramatically declines during estrus in mice, demonstrating that the local environment in the female reproductive tract can influence viral infectivity. The study provides an effective *in vivo* system for investigating the influence of physiological factors on HIV

infection and for testing the therapeutic potential of new strategies for intervention. Page 1292

## A Mafia mouse model for inherited retinal degeneration

Goldmann-Favre syndrome is an inherited eye disorder in which vision is weakened due to progressive retinal degeneration. Studies in both human patients and retinal degeneration mouse models have suggested that microglial cells play a role in pathogenesis; however, the underlying mechanism is unknown. In this study, Stephen Tsang and colleagues describe a novel mouse model in which the expression of circulating bone-marrow-derived microglial cells can be temporally and specifically controlled using the Mafia transgene. They report that ablation of the microglial cell population accelerates retinal degeneration, concomitant with an increase in the expression of certain inflammatory cytokines. These findings implicate inflammation as a key contributory factor in Goldmann-Favre syndrome and suggest potential targets for the development of therapies relevant to this and related neurodegenerative disorders. Page 1113

## Modelling *Candida* infection in zebrafish

*Candida albicans* is a common component of human gut and oral microbiota that can sometimes cause infections (candidiasis), particularly in immunocompromised

individuals. The effects of *Candida* overgrowth can vary from being relatively benign, as in oral or vaginal thrush, to manifesting as potentially life-threatening systemic infections. There are considerable gaps in the current understanding of host-pathogen interactions underlying candidiasis, in part due to the lack of suitable vertebrate models for intravital imaging. To address this, Robert Wheeler and colleagues have established a new zebrafish model for mucosal candidiasis. The group report that this *in vivo* model recapitulates several of the canonical features of mammalian candidiasis and displays gene expression patterns that confirm recent *in vitro* observations. Combined with the potential for non-invasive imaging, these findings indicate that zebrafish will complement existing models and provide new leverage for studying *Candida* infection. Page 1260

## Premature aging in telomerase-deficient zebrafish

Premature aging is a feature of the genetic disorder dyskeratosis congenita (DC). DC is caused by progressive shortening of telomeres, sequences that protect chromosome ends. Telomere shortening occurs in the normal process of aging, and mutations in telomerase, the enzyme that maintains telomere length, can accelerate this process. Although mouse models have

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provided insight into the role of telomeres in premature aging, they do not recapitulate all human symptoms. Here, María Cayuela's group show that telomerase-deficient zebrafish demonstrate the hallmark features of premature aging in the first generation, in contrast with mice, which have to be bred for several generations. Intriguingly, the zebrafish mutants show 'anticipation' (onset of disease at a younger age in the next generation), which is also apparent in individuals with DC. Reintroduction of telomerase is able to rescue telomere length, confirming the importance of telomerase dosage and paving the way for

studies of new therapeutics based on telomerase reactivation. **Page 1101**

### **Functional validation of GWAS hits for liver disease**

In recent years, genome-wide association studies (GWAS) have revealed associations between single-nucleotide polymorphisms (SNPs) and many human traits, including markers of disease. However, often the functional relevance of SNPs is unknown, and there is a need to develop rapid and effective methods to prioritise gene candidates for follow-up studies. Recently, a GWAS unveiled a suite of SNPs, mapping

to 42 gene loci, associated with liver disease. Here, Wolfram Goessling and colleagues utilised zebrafish to assess the importance of a subset of these candidates, selected based on the presence of zebrafish orthologues and possible links with liver biology as gleaned from database and literature searches. They show that eight candidates are likely to be important for liver homeostasis, because knockdown of these genes in zebrafish embryos impedes hepatocyte development and/or enhances susceptibility to injury. Future studies should focus on these loci to determine the molecular mechanisms underlying liver disease. **Page 1271**